

PCT

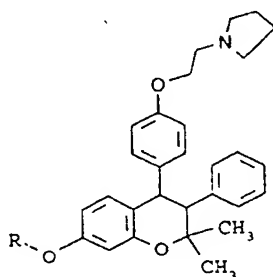
WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/40, 9/20		A1	(11) International Publication Number: WO 98/23270
			(43) International Publication Date: 4 June 1998 (04.06.98)
(21) International Application Number: PCT/DK97/00543 (22) International Filing Date: 26 November 1997 (26.11.97) (30) Priority Data: 1359/96 28 November 1996 (28.11.96) DK 1265/97 7 November 1997 (07.11.97) DK (71) Applicant: NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsværd (DK). (72) Inventor: RASMUSSEN, Stella, Rudkær; Borthigsgade 4, DK-2100 Copenhagen Ø (DK).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.	

(54) Title: PHARMACEUTICAL FORMULATION



(I)

(57) Abstract

The present invention relates to a pharmaceutical formulation for oral administration which comprises a compound of formula (I) wherein R is C₁₋₆ alkyl; or a pharmaceutically acceptable salt thereof, in combination with a hydrophilic binder and a water-soluble diluent.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China	KZ	Kazakhstan	PT	Portugal		
CU	Cuba	LC	Saint Lucia	RO	Romania		
CZ	Czech Republic	LI	Liechtenstein	RU	Russian Federation		
DE	Germany	LK	Sri Lanka	SD	Sudan		
DK	Denmark	LR	Liberia	SE	Sweden		
EE	Estonia			SG	Singapore		

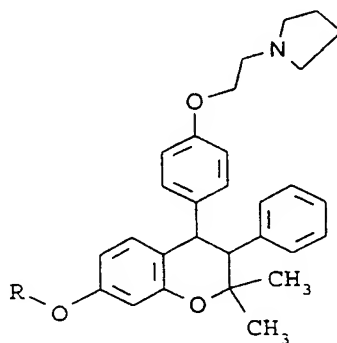
Title

Pharmaceutical formulation.

Field of the Invention

- 5 This invention relates to new pharmaceutical formulations for oral administration comprising certain 3,4-diarylchromans of formula I, or a pharmaceutically acceptable salt thereof, in combination with a hydrophilic binder and a water-soluble diluent.

The 3,4-diarylchromans of formula I



10

wherein R is C₁₋₆alkyl, and pharmaceutically acceptable salts thereof are known to be useful for reducing bone loss.

Background of the Invention

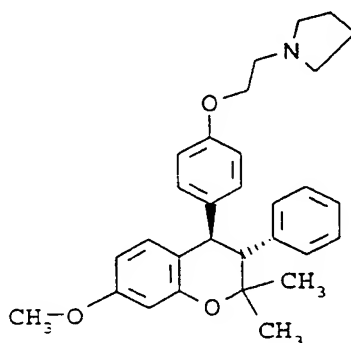
- 15 The formula I compounds are described in U.S. Patent No. 5,280,040. This patent describes the preparation of these compounds, as well as their use for reducing bone loss. The preparation of pharmaceutical compositions is also described.

20 Centchroman, which is 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-pyrrolidin-1-yl)ethoxy]phenyl]-7-methoxychroman, is a non-steroidal compound known to have antiestrogenic activity. It is in use in India as an oral contraceptive (see, for example, Salman *et al.*, U.S. Patent No. 4,447,622; Singh *et al.*, *Acta Endocrin (Copenh)* **126** (1992), 444 - 450; Grubb, *Curr Opin Obstet Gynecol* **3** (1991), 491 - 495; Sankaran

et al., Contraception 9 (1974), 279 - 289; Indian Patent Specification No. 129187). Centchroman has also been investigated as an anti-cancer agent for treatment of advanced breast cancer (Misra et al., Int J Cancer 43 (1989), 781 - 783. Recently, centchroman as a racemate has been found as a potent cholesterol lowering
5 pharmaceutical agent expressed by a significant decrease of the serum concentrations (S.D. Bain et al., J Min Bon Res 9 (1994), S 394).

Levormeloxifene, (-) - 3R,4R - trans- 7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}chromane, is a particular preferred compound from this series of 3,4-diarylchromans. Levormeloxifene may be used in human and
10 veterinary medicine for the regulation of bone metabolism. It may be used, for example, in the treatment of patients suffering from bone loss due to osteoporosis (including post-menopausal osteoporosis and glucocorticoid-related osteoporosis), Paget's disease, hyperparathyroidism, hypercalcemia of malignancy and other conditions characterized by excessive rates of bone resorption and/or decreased rates
15 of bone formation.

The 3,4-diarylchromans are prepared according to known methods, such as those disclosed in U.S. Patent No. 3,340,276 to Carney et al., U.S. Patent No. 3,822,287 to Bolger, and Ray et al., J Med Chem 19 (1976), 276 - 279, the contents of which are incorporated herein by reference. Conversion of the cis isomer to the
20 trans configuration by means of an organometallic base-catalyzed rearrangement is disclosed in U.S. Patent No. 3,822,287. The optically active d- and l-enantiomers may be prepared as disclosed by Salman et al. in U.S. Patent No. 4,447,622 (incorporated herein by reference) by forming an optically active acid salt which is subjected to alkaline hydrolysis to produce the desired enantiomer. The resolution
25 of (+/-) - 3,4-trans-7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}chromane in its optical antipodes is described in U.S. Patent No. 4,447,622 incorporated herein by reference. Example 1 of U.S. Patent No. 4,447,622 describes the preparation of the minus enantiomer, shown by formula It :



(II)

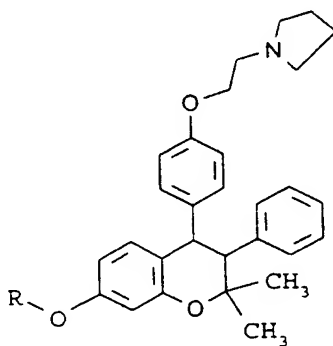
(In this specification, the compound of formula II is referred to as levormeloxifene.) In example 2 of U.S. Patent No. 4,447,622, levormeloxifene is obtained as the free base and the hydrochloride salt.

The compounds of formula I may be administered as pharmaceutically acceptable salts. A particularly useful pharmaceutically acceptable salt of levormeloxifene is the hydrogen fumarate salt (in this specification, this compound is referred to as levormeloxifene fumarate.). This salt form is prepared by dissolving fumaric acid and (-)-3R,4R- trans - 7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}chromane in a common solvent such as e.g. methanol, and crystallizing the resulting salt from the solution.

An object of the present invention is to provide a pharmaceutical formulation for oral administration which formulation has a favourable bioavailability.

The present invention provides a pharmaceutical formulation for oral administration comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, in combination with a hydrophilic carrier composition. Such formulations have an increased solubility in aqueous media.

The present invention provides a pharmaceutical formulation for oral administration which comprises a compound of formula I



(I)

wherein R is C₁₋₆alkyl; or a pharmaceutically acceptable salt thereof, a hydrophilic binder and a water-soluble diluent. According to a preferred embodiment of the invention, the formulation further comprises a surfactant. The present invention also provides pharmaceutical formulations further comprising a lubricant and/or disintegrant. To further improve the stability of the formulation according to the invention, a suitable antioxidant or a combination of antioxidants may be used. It is preferred to use the compounds of formula I in the trans configuration. The enantiomeric forms are preferred over racemic mixtures. Within particularly preferred embodiments, R is methyl.

The general chemical terms used in the above formula have their usual meanings.

As used herein, the term "C₁₋₆alkyl" includes straight and branched chain alkyl radicals containing from 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, n-amyl, sec-amyl, n-hexyl, 2-ethylbutyl, 2,3-dimethylbutyl and the like.

The term "pharmaceutically acceptable salt" represents salt forms of a compound of formula I that are physiologically suitable for pharmaceutical use. The pharmaceutically acceptable salts can exist in conjunction with a compound of formula I as acid addition primary, secondary, tertiary, or quaternary ammonium, alkali metal, or alkaline earth metal salts. Generally, the acid addition salts are prepared by the reaction of an acid with a compound of formula I, wherein R is as defined previously. The alkali metal and alkaline earth metal salts are generally

prepared by the reaction of the metal hydroxide of the desired metal salt with a compound of formula I, wherein R is hydrogen.

Within the present invention, the compounds of formula I may be prepared in the form of pharmaceutically acceptable salts, especially acid-addition salts,

5 including salts of organic acids and mineral acids. Examples of such salts include salts of organic acids such as formic acid, fumaric acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, succinic acid, malic acid, tartaric acid, citric acid, benzoic acid, salicylic acid and the like. Suitable inorganic acid-addition salts include salts of hydrochloric, hydrobromic, sulphuric and phosphoric
10 acids and the like. The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

The term "hydrophilic binder" represents binders commonly used in the
15 formulation of pharmaceuticals, such as polyvinylpyrrolidone, copolyvidone (cross-linked polyvinylpyrrolidone), polyethylene glycol, sucrose, dextrose, corn syrup, polysaccharides (including acacia, tragacanth, guar, and alginates), gelatin, and cellulose derivatives (including hydroxypropyl methylcellulose, hydroxypropyl cellulose, and sodium carboxymethylcellulose).

20 The term "water-soluble diluent" represents compounds typically used in the formulation of pharmaceuticals, such as sugars (including lactose, sucrose, and dextrose), polysaccharides (including dextrans and maltodextrin), polyols (including mannitol, xylitol, and sorbitol), and cyclodextrins.

The term "non water-soluble diluent" represents compounds typically used in
25 the formulation of pharmaceuticals, such as calcium phosphate, calcium sulfate, starches, modified starches and microcrystalline cellulose.

The term "non water-soluble diluent with non-swelling properties" represents the non water-soluble diluents as indicated above, but excluding starches and modified starches and the like.

30 The term "surfactant", as used herein, represents ionic and nonionic surfactants or wetting agents commonly used in the formulation of pharmaceuticals, such as ethoxylated castor oil, polyglycolized glycerides, acetylated monoglycerides,

sorbitan fatty acid esters, poloxamers, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene derivatives, monoglycerides or ethoxylated derivatives thereof, diglycerides or polyoxyethylene derivatives thereof, sodium docusate, sodium laurylsulfate, cholic acid or derivatives thereof, lecithins, alcohols and phospholipids.

5 The term "antioxidant" represents the three groups of antioxidants, true antioxidants, reducing agents and antioxidant synergists, such as tocopherols, tocopherolesters, alkyl gallates, butylated hydroxyanisole, butylated hydroxytoluene, ascorbic acid, citric acid, edetic acid and its salts, lecithin and tartaric acid.

10 The term "disintegrant" represents compounds such as starches, clays, celluloses, alginates, gums, cross-linked polymers (such as cross-linked polyvinylpyrrolidone and cross-linked sodium carboxymethylcellulose), sodium starch glycolate, low-substituted hydroxypropyl cellulose, and soy polysaccharides. Preferably, the disintegrant is a modified cellulose gum such as e.g. cross-linked sodium carboxymethylcellulose.

15 - The term "lubricant" represents compounds frequently used as lubricants or glidants in the preparation of pharmaceuticals, such as talc, magnesium stearate, calcium stearate, stearic acid, colloidal silicon dioxide, magnesium carbonate, magnesium oxide, calcium silicate, microcrystalline cellulose, starches, mineral oil, waxes, glyceryl behenate, polyethylene glycol, sodium benzoate, sodium acetate, 20 sodium chloride, sodium laurylsulfate, sodium stearyl fumarate, and hydrogenated vegetable oils. Preferably, the lubricant is magnesium stearate or talc, more preferably magnesium stearate and talc in combination.

25 All formulations of the present invention have an increased solubility in aqueous media and therefore, greater bioavailability would be expected. In a bioavailability study in humans comparing a solution of levormeloxifene and a levormeloxifene tablet formulation a bioequivalency of 100% was obtained.

 In one preferred embodiment of the invention, the hydrophilic binder is gelatin, cellulose derivative, polyvinylpyrrolidone or copolyvidone.

30 In another preferred embodiment of the invention, the water-soluble diluent is a sugar, a polysaccharide or cyclodextrin.

 In another preferred embodiment of the invention, the formulation further comprises a non water-soluble diluent. In one embodiment thereof the non water-

soluble diluent is a non water-soluble diluent with non-swelling properties, preferably microcrystalline cellulose.

In another preferred embodiment of the invention, the formulation further comprises an antioxidant. Preferably the antioxidant is tocopherols and
5 tocopherolesters, such as alpha-tocopherol succinate.

In another preferred embodiment of the invention, the formulation further comprises a surfactant. When the surfactant is present, preferably it is an anionic or nonionic surfactant. Representative surfactants from this preferred group include
10 sodium laurylsulfate, polyglycolized glycerides, polyoxyethylene sorbitan fatty acid esters, monoglycerides, diglycerides or glycerol.

In another preferred embodiment of the invention, the formulation further comprises a lubricant(s) and/or a disintegrant.

Certain formulations of the present invention are more preferred. More preferably, the hydrophilic binder is polyvinylpyrrolidone or copolyvidone. More
15 preferably, the water-soluble diluent is a sugar, such as lactose, sucrose, dextrose. More preferably, the surfactant is a nonionic surfactant, such as polyoxyethylene sorbitan fatty acid esters or glycerol.

Certain formulations of the present invention are most preferred. Most preferably, the hydrophilic binder is copolyvidone. Most preferably, the water-soluble
20 diluent is lactose. Most preferably, the surfactant, when present, is glycerol.

The amount of hydrophilic binder in the pharmaceutical formulation according to the invention is preferably from about 1% to about 25% (w/w), more preferably from about 1% to about 15% (w/w), most preferably from about 2,5% to about 15% (w/w).

25 The amount of water-soluble diluent in the pharmaceutical formulation according to the invention is preferably from about 20% to about 98% (w/w), more preferred from about 20% to about 80% (w/w).

The amount of non water-soluble diluent in the pharmaceutical formulation according to the invention is preferably from about 1% to about 50% (w/w), more
30 preferred from about 5% to about 30% (w/w).

The amount of the compound of formula I in the pharmaceutical formulation according to the invention is preferably from about 0,05% to about 50% (w/w), such as from about 0,1% to about 40% (w/w).

The orally administerable formulations of the present invention are prepared and administered according to methods well known in pharmaceutical chemistry, see Remington's Pharmaceutical Sciences, 17th ed. (A. Osol ed., 1985). For example, the compositions of the present invention may be administered by means of solid dosage forms such as tablets and capsules. Preferably, the compositions are formulated as tablets. These tablets may be prepared by wet granulation, by dry granulation, or by direct compression.

Tablets for this invention are prepared utilizing conventional tableting techniques. A general method of manufacture involves blending of a compound of formula I, or a salt thereof, the water-soluble diluent, hydrophilic binder and optionally a portion of a disintegrant. This blend is then granulated with an aqueous solution of the hydrophilic binder or an aqueous solution of the hydrophilic binder and surfactant and milled, if necessary. The granules are dried and reduced to a suitable size. Any other ingredients, such as lubricants, (e.g. magnesium stearate) and additional disintegrants, are added to the granules and mixed. This mixture is then compressed into a suitable size and shape using conventional tableting machines such as a rotary tablet press. The tablets may be film coated by techniques well known in the art.

Capsules for this invention are prepared utilizing conventional methods. A general method of manufacture involves blending of a compound of formula I, or a salt thereof, the water-soluble diluent, a hydrophilic binder, and optionally a portion of a disintegrant. This blend is then granulated with an aqueous solution of the hydrophilic binder or an aqueous solution of the hydrophilic binder and surfactant in water, and milled, if necessary.

The granules are dried and reduced to a suitable size. Any other ingredients, such as a lubricant, are added to the granules and mixed. The resulting mixture is then filled into a suitable size hard-shell gelatin capsule using conventional capsule-filling machines.

The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way.

The preferred range of pharmaceutical formulation (such as solid dosage form, e.g. capsule or tablet) strength may be from about 0.125 mg to about 40 mg of
5 a compound of formula I, more preferred from about 0.25 mg to about 5 mg of a compound of formula I, preferably levormeloxifene.

The preferred range of total mass may be from about 40 mg to about 500 mg depending on the strength of the formulation, more preferred from about 80 mg to about 320 mg.

10 Tablets and capsules may be prepared using the ingredients and procedures as described below:

Formulation 1

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 10 mg base	12.54 mg
Microcrystalline cellulose	48.00 mg
Cross-carmellose sodium	25.00 mg
Copolyvidone	24.00 mg
Lactose	206.00 mg
Magnesium stearate	1.00 mg
Talc	3.20 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 320 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 1.25 mg to 40 mg with a total mass of 320 mg.

Formulation 2

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 5 mg base	6.27 mg
Microcrystalline cellulose	24.00 mg
Cross-carmellose sodium	12.50 mg
Copolyvidone	12.00 mg
Lactose	102.85 mg
Magnesium stearate	0.80 mg
Talc	1.60 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous

solution of copolyvidone. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 160 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 0.25 mg to 5 40 mg with a total mass of 160 mg.

Formulation 3

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 5 mg base	6.27 mg
Microcrystalline cellulose	18.00 mg
Cross-carmellose sodium	9.36 mg
Copolyvidone	9.00 mg
Lactose	75.57 mg
Magnesium stearate	0.60 mg
Talc	1.20 mg

10 The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 320 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 0.125 mg to 15 20 mg with a total mass of 120 mg.

Formulation 4

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 40 mg base	50.00 mg
Microcrystalline cellulose	48.00 mg
Cross-carmellose sodium	25.00 mg
Copolyvidone	24.00 mg
Na-laurylsulfate	6.40 mg
Lactose	161.80 mg
Magnesium stearate	1.60 mg
Talc	3.20 mg

- The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, and a
- 5 portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone containing dissolved sodium laurylsulfate. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 320 mg. It is possible to manufacture
- 10 levormeloxifene tablet strengths in the range of 1.25 mg to 40mg with a total mass of 320 mg.

Formulation 5

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 40 mg base	50.00 mg
Dextrose	168.20 mg
Microcrystalline cellulose	48.00 mg
Cross-carmellose sodium	25.00 mg -
Copolyvidone	24.00 mg
Magnesium stearate	1.60 mg
Talc	3.20 mg

The mixture of levormeloxifene fumarate, dextrose, microcrystalline cellulose, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 320 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 1.25 mg to 40 mg with a total mass of 320 mg.

10 Formulation 6

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 40 mg base	50.00 mg
Microcrystalline cellulose	70.00 mg
Cross-carmellose sodium	31.25 mg
Gelatine	5.00 mg
Lactose	237.75 mg
Magnesium stearate	2.00 mg
Talc	4.00 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, and a portion of cross-carmellose sodium is granulated with an aqueous solution of gelatine. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 400 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 1.25 mg to 40 mg with a total mass of 400 mg.

Formulation 7

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 40 mg base	50.00 mg
Microcrystalline cellulose	70.00 mg
Cross-carmellose sodium	31.25 mg
Dextrose	237.75 mg
Gelatine	5.00 mg
Magnesium stearate	2.00 mg
Talc	4.00 mg

The mixture of levormeloxifene fumarate, dextrose, microcrystalline cellulose, and a portion of cross-carmellose sodium is granulated with an aqueous solution of gelatine. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 400 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 1.25 mg to 40 mg with a total mass of 400 mg.

Formulation 8

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 40 mg base	50.00 mg
Microcrystalline cellulose	60.00 mg
Cross-carmellose sodium	31.25 mg
Copolyvidone	25.00 mg
Tween 80	3.25 mg
Lactose	224.50 mg
Magnesium stearate	2.00 mg
Talc	4.00 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone containing Tween 80. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 400 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 1.25 mg to 40 mg with a total mass of 400 mg.

Formulation 9

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 40 mg base	50.00 mg
Microcrystalline cellulose	60.00 mg
Cross-carmellose sodium	31.25 mg
Copolyvidone	29.00 mg
Glycerol	3.25 mg
Lactose	220.50 mg
Magnesium stearate	2.00 mg
Talc	4.00 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone containing glycerol. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 400 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 1.25 mg to 40 mg with a total mass of 400 mg.

Formulation 10

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 40 mg base	50.00 mg
Microcrystalline cellulose	68.00 mg
Cross-carmellose sodium	26.25 mg
Gelatine	5.00 mg
Glycerol	6.25 mg
Dextrose	338.50 mg
Magnesium stearate	2.00 mg
Talc	4.00 mg

The mixture of levormeloxifene fumarate, dextrose, microcrystalline cellulose, and a portion of cross-carmellose sodium is granulated with an aqueous solution of gelatine and glycerol. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 400 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 1.25 mg to 40 mg with a total mass of 400 mg.

Formulation 11

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 40 mg base	50.00 mg
Microcrystalline cellulose	35.00 mg
Cross-carmellose sodium	26.25 mg
hydroxypropyl-betacyclodextrin (HP-cd)	115.00 mg
Gelatine	5.00 mg
Glycerol	6.25 mg
Dextrose	256.50 mg
Magnesium stearate	2.00 mg
Talc	4.00

5 The mixture of levormeloxifene fumarate, dextrose, hydroxypropyl-betacyclodextrin
 microcrystalline cellulose, and a portion of cross-carmellose sodium is granulated
 with an aqueous solution of gelatine containing glycerol. The granules are dried,
 reduced to a suitable size and mixed with magnesium stearate, talc and remaining
 cross-carmellose sodium. The mixture is compressed into individual tablets yielding a
 10 tablet weight of 500 mg. It is possible to manufacture levormeloxifene tablet
 strengths in the range of 1.25 mg to 80 mg with a total mass of 500 mg.

Formulation 12 and 13

Ingredient	Weight
Levormeloxifene fumarate corresponding to 5 mg base	6.27 mg
Lactose	395.1 mg
Microcrystalline cellulose	9.875 mg -
Polyvinylpyrrolidone/copolyvidone	8.400 mg
Magnesium stearate	0.375 mg

The mixture of levormeloxifene fumarate, lactose and microcrystalline cellulose is granulated with an aqueous solution of polyvinylpyrrolidone or copolyvidone. The granules are dried, reduced to a suitable size and mixed with magnesium stearate. The mixture is then filled into size 0 hard-shell gelatine capsules utilizing

- 5 conventional encapsulating equipment. In order to obtain different capsule strenghts in the range of 1.25 mg to 20.0 mg, different quantities are weighed out in the range of 15 mg to 240 mg.

Formulation 14

10

Ingredient	Weight (mg/tablet)
Levormeloxifene fumarate corresponding to 0.25 mg base	0.313 mg
Microcrystalline Cellulose	12.00 mg
Cross-Carmellose Sodium	6.25 mg
Copolyvidone	6.00 mg
Lactose	54.20 mg
Alpha-tocopherol Succinate	0.0308 mg
Magnesium Stearate	0.40 mg
Talc	0.80 mg

- The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, antioxidant, and a portion of cross-carmellose sodium and copolyvidone is
- 15 granulated with an aqueous solution of copolyvidone. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 80 mg. It is possible to manufacture levormeloxifene tablet strenghts in the range of 0.125 mg to 10 mg with a total mass of 80 mg.

20

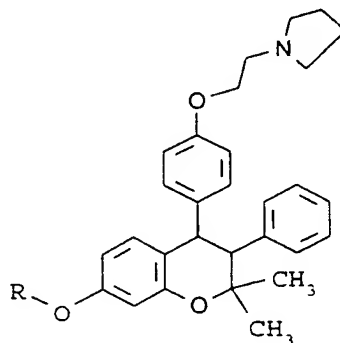
Formulation 15

Ingredient	Weight (mg/tablet)
Levormeloxifene fumarate corresponding to 0.25 mg base	3.13 mg
Microcrystalline Cellulose	15.00 mg
Cross-Carmellose Sodium	7.75 mg
Copolyvidone	7.50 mg
Lactose	64.80 mg
Alpha-tocopherol Succinate	0.0308 mg
Magnesium Stearate	0.50 mg
Talc	1.00 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, antioxidant, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 100 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 0.125 mg to 20 mg with a total mass of 100 mg.

Claims

1. A pharmaceutical formulation for oral administration which comprises a compound of formula I



(I)

wherein R is C₁₋₆alkyl; or a pharmaceutically acceptable salt thereof, in combination with a hydrophilic binder and a water-soluble diluent.

2. The formulation according to claim 1 wherein said hydrophilic binder is copolyvidone or cross-linked polyvinylpyrrolidone.
3. The formulation according to Claim 1 or 2 wherein said water-soluble diluent is lactose.
4. The formulation according to any one of Claims 1-3 further comprising a surfactant.
5. The formulation according to Claim 4 wherein said surfactant is glycerol.
6. The formulation according to any one of the preceding claims comprising a compound of formula I, lactose, copolyvidone, talc, magnesium stearate, microcrystalline cellulose and cross-carmellose sodium.

7. The formulation according to any one of the preceding claims further comprising an antioxidant.

5 8. The formulation according to claim 7 wherein said antioxidant is alpha-tocopherol succinate.

9. The formulation according to any one of the preceding claims further comprising a non water-soluble diluent.

10

10. The formulation according to claim 9 wherein said non water-soluble diluent is microcrystalline cellulose.

11. The formulation according to any one of the preceding claims wherein said
15 formulation is a solid dosage form.

12. The formulation according to claim 11 wherein said dosage form is a tablet.

13. The formulation according to any one of the preceding claims further
20 comprising a film coating.

14. The formulation according to any one of the preceding claims wherein R in the compound of formula I is methyl.

25 15. The formulation according to any one of the preceding claims wherein said compound of formula I is in the trans configuration.

16. The formulation according to any one of the preceding claims wherein said
30 compound of formula I is 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-pyrrolidin-1-yl)ethoxy]phenyl]-7-methoxychroman or a salt thereof.

17. The formulation according to any one of the preceding claims wherein said compound of formula I is an isolated l-enantiomer or a salt thereof.

18. The formulation according to any one of the preceding claims wherein said
5 compound of formula I is (-) - 3R,4R - trans- 7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}chromane or a salt thereof.

19. The formulation according to claim 18 wherein said compound of formula I is in the form of the hydrogen fumarate salt.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 97/00543

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/40, A61K 9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5407955 A (HENRY U. BRYANT ET AL), 18 April 1995 (18.04.95), see column 11 and 12 --	1-19
X	US 5482958 A (HENRY U. BRYANT ET AL), 9 January 1996 (09.01.96), see column 11 and 12 --	1-19
X	US 5472977 A (HENRY U. BRYANT ET AL), 5 December 1995 (05.12.95), see column 11 and 12 --	1-19
X	US 5563133 A (PHILIP A. HIPSKIND), 8 October 1996 (08.10.96), see formulation example 4 and 11 --	1-19

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

25 February 1998

Date of mailing of the international search report

03 -03- 1998

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. +46 8 666 02 86

Authorized officer

Göran Karlsson
Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 97/00543

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4447622 A (MOHAMMAD SALMAN ET AL), 8 May 1984 (08.05.84) --	1-19
A	US 5464862 A (VIRENDER M. LABROO ET AL), 7 November 1995 (07.11.95) -- -----	1-19

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

03/02/98

International application No.

PCT/DK 97/00543

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5407955 A	18/04/95	CA 2142513 A	19/08/95
		EP 0672412 A	20/09/95
		JP 7258080 A	09/10/95
		US 5453442 A	26/09/95
		US 5472977 A	05/12/95
		US 5482958 A	09/01/96
US 5482958 A	09/01/96	US 5453442 A	26/09/95
		CA 2142513 A	19/08/95
		EP 0672412 A	20/09/95
		JP 7258080 A	09/10/95
		US 5407955 A	18/04/95
		US 5472977 A	05/12/95
US 5472977 A	05/12/95	CA 2142513 A	19/08/95
		EP 0672412 A	20/09/95
		JP 7258080 A	09/10/95
		US 5407955 A	18/04/95
		US 5453442 A	26/09/95
		US 5482958 A	09/01/96
US 5563133 A	08/10/96	CA 2162786 A	23/05/96
		EP 0714891 A	05/06/96
US 4447622 A	08/05/84	NONE	
US 5464862 A	07/11/95	AU 674394 B	19/12/96
		AU 1639497 A	22/05/97
		AU 6230294 A	26/09/94
		BR 9405843 A	16/01/96
		CA 2157879 A	12/09/94
		CZ 9502320 A	17/04/96
		EP 0688214 A	27/12/95
		HU 74575 A	28/01/97
		HU 9502624 D	00/00/00
		JP 8506346 T	09/07/96
		NO 953542 A	08/09/95
		NZ 262569 A	22/08/97
		US 5280040 A	18/01/94
		WO 9420098 A	15/09/94